Indium tribromide-promoted arene-terminated epoxy olefin cyclization†‡

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An arene-terminated epoxy olefin cyclization was promoted by a water-tolerant Lewis acid to give tri- and tetracyclic 3β-hydroxy terpenoids and steroid derivatives in 57 and 37% yields, respectively, per new formed ring up to 75%.

The biomimetic cyclization of polyalkenes to steroids and their precursors continue to be of both mechanistic and synthetic interest.[1] Sulfonate esters, trisubstituted olefins, allylic alcohols, acetals and epoxides had been used as initiating groups for these cascade cyclizations.[2] Among them, epoxide has been one of the most popular initiators. 2,3-Oxidosqualene had been identified as a genuine intermediate in the conversion of squalene to lanosterol.[3] Mimicking this natural transformation, Corey, van Tamelen and Goldsmith, among others, have exploited the acid-promoted cascade cyclization of epoxy olefins as a very useful strategy for the building of polycyclic terpenoids.[4] However, the catalysts typically employed are sensitive to moisture, difficult to handle and the yields (about 20%)[4b,6a] are not satisfactory. In this Communication, we report a mild, convenient and simple procedure for investigating water-tolerant Lewis acid-promoted epoxy olefin cyclizations to prepare arene-terminated 3-hydroxy terpenoid and steroid derivatives.

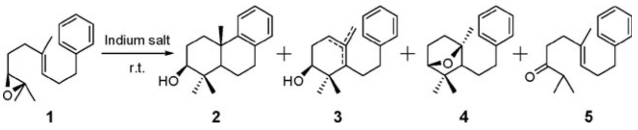
There are numerous reports[5] regarding the isolation and biological data of polycyclic compounds containing a 3-hydroxy group and one terminal aromatic ring. However, there have been very few reported synthetic studies of these structures.[6] As far as we know, there have been no reports on Lewis acid-promoted epoxy olefin cyclizations in aqueous media. Recently, we embarked upon Lewis acid-promoted polyene cyclizations[7] and the development of water-tolerant Lewis acidic indium salt-mediated reactions leading to the formation of various carbon–carbon bonds.[8] These results prompted us to investigate Lewis acid-mediated epoxy olefin cyclizations in aqueous environments.

Preliminary studies focused on the cyclization of **1** using various Lewis acids in organic solvents. The results are summarized in Table 1. We were gratified to find that, with the exception of indium trifluoride, indium salts do indeed promote fast epoxy olefin cyclization in high yields and with good selectivities (Table 1). Among the screened solvent systems, DCM was the solvent of choice (Table 1, entry 7). As shown in Table 1, with a concentration of 0.1 M in DCM, the epoxy olefin cyclization proceeded smoothly at ambient temperature and in the open air, furnishing the target tricyclic product, accompanied by a monocyclic alkene, an oxabicycloalkane and a ketone. In terms of yield and selectivity of the tricyclic product, indium tribromide is the most promising Lewis acid.

Even 0.2 equivalents of indium tribromide is efficient enough to give a combined yield of up to 86%, with the tricyclic compound as the major product (Table 1, entry 3). The yield and selectivity can be further increased if more indium tribromide is used (Table 1, entries 6 and 7).

Encouraged by the remarkable results obtained with the above reaction conditions, and in order to show the generality and scope of this new protocol, we explored the reaction with various substituted aromatic terminators. The results are summarized in Table 2. In all cases, the tricyclic products were obtained in good yields of up to 57%, per new formed ring up to 75% (Table 2, entry 1). According to Yamamoto's strategy, the monocyclic alkene can be further converted into the tricyclic products.[9] When 3-methoxybenzene was used as the terminator, two kinds of tricyclic products were obtained

Table 1 Indium salt-promoted epoxy olefin cyclization[a]



Entry	Solvent	Catalyst/equiv.	Yield (%)[b] 2	3	4	5
1	CH_2Cl_2	InF_3/0.2	Trace	Trace	Trace	Trace
2	CH_2Cl_2	$InCl_3$/0.2	45	8	12	4
3	CH_2Cl_2	$InBr_3$/0.2	50	11	17	8
4	CH_2Cl_2	InI_3/0.2	35	8	9	14
5	CH_2Cl_2	$In(OTf)_3$/0.2	28	27	8	12
6	CH_2Cl_2	$InBr_3$/0.5	54	11	18	9
7	**CH_2Cl_2**	**$InBr_3$/2**	**57**	**10**	**19**	**Trace**
8	CH_3NO_2	$InBr_3$/2	54	9	17	8
9	Toluene	$InBr_3$/2	40	7	20	Trace
10	CH_3CN	$InBr_3$/2	Trace	12	Trace	Trace
11	$CHCl_3$	$InBr_3$/2	52	11	21	5
12	Et_2O	$InBr_3$/2	Trace	12	Trace	14

[a] All reactions were performed with **1** (0.1 mmol) and Lewis acid in 1 ml of solvent at room temperature for 1 h. [b] Isolated yield.

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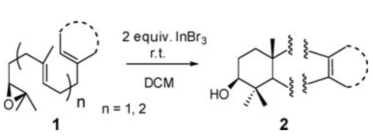
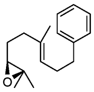
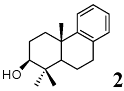
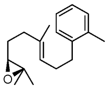
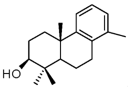
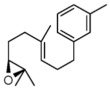
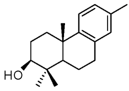
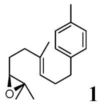
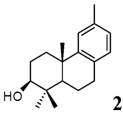
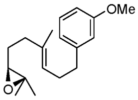
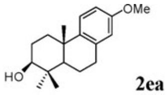
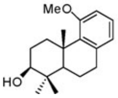
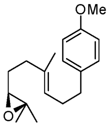
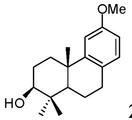
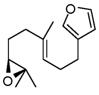
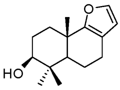
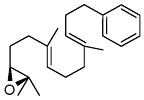
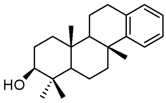
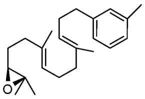
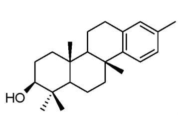
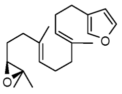
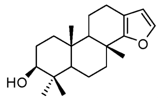
† This paper is dedicated to Professor E. J. Corey on the occasion of his 80th birthday.

‡ Electronic supplementary information (ESI) available: Detailed experimental procedures, ^1H and ^{13}C NMR data, and analytical data for all compounds. See DOI: 10.1039/b718337b

Table 2 Indium tribromide-promoted epoxy olefin cyclization for the preparation of polycyclic compounds[a]



Entry	Epoxy olefin	Product	Yield (%)[b]
1	 **1a**	 **2a**	57 (40[c])
2	 **1b**	 **2b**	54
3	 **1c**	 **2c**	51 (30[c])
4	 **1d**	 **2d**	51
5	 **1e**	 **2ea**  **2eb**	77[d]
6	 **1f**	 **2f**	58 (31[c])
7	 **1g**	 **2g**	52[e]
8	 **1h**	 **2h**	35
9	 **1i**	 **2i**	31
10	 **1j**	 **2j**	37[e]

[a] All reactions were performed with **1** (0.1 mmol) and 2 equivalents of InBr$_3$ in 1 ml of solvent at room temperature for 1 h unless otherwise stated. [b] Isolated yield. [c] Reactions were carried out with **1** (0.1 mmol) in 1 ml DCM/H$_2$O (10 : 1) in the presence of 4 equivalents of InBr$_3$. [d] The combined yield of **2ea** and **2eb**; the ratio of **2ea** : **2eb** was 37 : 40. [e] 0.2 equivalents of InBr$_3$ were used.

in a combined yield of 77% (Table 2, entry 5). However, only one tricyclic product was formed when 3-methoxy was replaced by 3-methyl (Table 2, entry 3). This may be due to strong steric hindrance between the 3-methyl and angular methyl groups, which prohibits one of the two cyclization pathways.

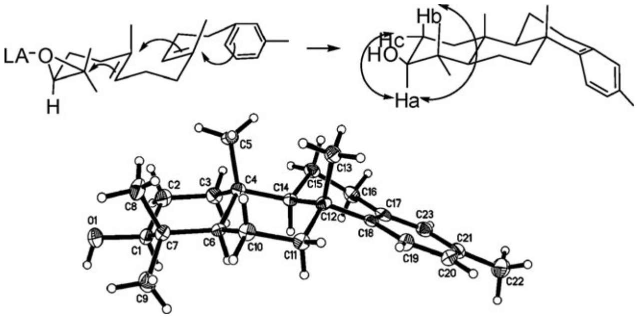
To demonstrate the applicability and versatility of this synthetic strategy, we further extended this method to the preparation of tetracyclic compounds (Table 2, entries 8, 9 and 10). The indium tribromide-catalyzed epoxy olefin cyclization afforded the tetracyclic products in yields of up to 35%, per new formed ring up to 70% (Table 2, entry 8).

Furan-terminated polycyclic compounds have been used as important intermediates in the synthesis of terpenes.[10] Both in tri- and tetracyclizations, furyl terminators are much reactive than phenyl terminators as the furyl group is more electron rich. In the presence of 0.2 equivalents of indium tribromide, furan-terminated epoxide olefin cyclization proceeded smoothly to give tri- and tetracyclic products in 52 and 37% yields, respectively (Table 2, entries 7 and 10).

To mimic the mild reaction conditions of the biosynthesis of steroids and terpenoids, we tested this cyclization in aqueous media with the water-tolerant Lewis acid indium tribromide as the catalyst. To our delight, the cyclization proceeded well in aqueous media, albeit in decreased yields (Table 2, entries 1, 3 and 6).

According to the Stork–Eschenmoser hypothesis,[2e–g] the pre-organized chair–chair–chair conformation is important to the diastereoselectivity. Lewis acid-promoted epoxide ring opening initiated the cascade antiparallel addition of the olefins, furnishing the *trans*,*trans*-tetracyclized products with excellent regio- and diastereoselectivity. Five chiral centers are created in a single operational step, and only 2 out of 32 possible isomers are formed (Scheme 1). The relative stereochemical configurations of the products were determined by detailed 1D- and 2D-NMR, and by X-ray analysis.[12] The stereochemistry of the 3-OH group (β-face) was further assigned from the coupling constant between 3-CH$_a$ and 2-CH$_{2(b,c)}$ ($^3J_{\mathrm{H_{axial}-H_{axial}}} \approx$ 11 Hz, $^3J_{\mathrm{H_{axial}-H_{equatorial}}} \approx$ 5 Hz). The physical and spectroscopic properties of **2a**, **2f**, **2g** and **2h**, obtained in our conversions, were identical with those reported previously.[6a,11]

In conclusion, we have reported the first indium tribromide-promoted epoxide ring opening-initiated and arene-terminated polyene cyclization. This procedure offers several advantages,



Scheme 1 X-Ray crystallographic structure of **2i**; 50% probability was chosen for the ellipsoids.[12]

including easy handling, mild conditions, high selectivity and improved yields, which make it a useful and attractive strategy for the synthesis of steroid and terpenoid derivatives. In addition, this reaction can be carried out in aqueous media. Further work to design a better catalyst to effect the reaction in aqueous environments is in progress.

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Notes and references

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12 CCDC 669258 and 669259 contain the supplementary crystallographic data of **2h** and **2i**. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b718337b.